SECTION 2. GMPs for ATMPS: general principles	Q1: Are the principles laid down in Section 2 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?). Please provide comments on the text below as appropriate
	Answer: Yes, they are. **Comments**: Lines 81 to 93. All the objectives included are the same of other quality systems like JACIE.
	Q2.Do you consider it useful that additional level of detail regarding the application of the risk-based approach is provided in the Guideline? In the affirmative, please provide examples.
	Answer: Yes, we consider it would be useful additional level of detail regarding the application. Different requirements related to facilities, characterization, quality controls or release criteria, among others, according to the type of products should be introduced: a) Non substantially manipulated ATMPs a. Autologous b. Allogeneic b) Substantially manipulated ATMPs a. Autologous b. Allogeneic 1. When the only manipulation is cell expansion 2. When the manufacturing process includes pluripotent stem cells: using reprogramming techniques (iPS cells) or not (hES cells) 3. When the manufacturing process includes genetic modification **Comments**: 1. Lines 103 to 114. It is very important the explicit recognition that ATMPs are not a single type of medicinal product and the great variability in terms of associated risks. Nevertheless it is not enough to recognize the necessity of flexibility. The GMPs for ATMPs should incorporate specific different requirements according to the type of product, its origin and its manipulation (e.g. differences in terms of characterization and quality controls). Some examples: – In case of non substantially manipulated products, quality controls should met JACIE standards. – In case of autologous products only subject to cell expansion (and a low number of doublings) some of the quality controls, such as karyotype, should only be required during the validation process but not in every single batch. Another example refers to the characterization tests, such as potency tests, which might be challenging for some autologous products due to the variability patient-to-patient and which may not easily be definable by a single value due to the complexity of composition.

	– In autologous products the subject-to-subject variability should be considered when establishing criteria for approval of starting materials. In early phases of clinical research (clinical trial phases I/II) it should be allowed wider ranges in the starting materials specifications. The necessity of process standardization to make the manufacturing process as reproducible as possible, usually leads to set as much detailed as possible specifications with narrow ranges for acceptance criteria. Some ethical issues can arise as a consequence (for example when patients have undergone surgery and have no other therapeutic options). Making the requirements more flexible in the early phases will help patients to benefit from these novel therapies. 2. Lines 115 to 122. It is also very important the explicit recognition of the required flexibility for early phases of clinical trials, but it is required more specific details to facilitate the flexibility. If not, every National Competent Authority will ask for requirements according to their understanding what might result in wide differences between countries in the UE. Several examples: – The continuously monitoring of pressure requirement might not be required for early stages of development (phase I/II clinical trials) provided the pressure is frequently monitored and recorded according to the activity. – In first steps of the manufacturing processes of a single batch of ATMPs, small volume of culture media and supplements are needed. To optimize its use, aliquots should be allowed. Quality controls of these aliquots, if required, should be proportionate as the quality of the raw material is certified and quality controls are performed at different stages of the manufacturing process as well as in the finished product. – It should be explicitly allowed the use of research-grade raw materials at early stages of development. Sometimes there are no GMP grade raw materials and in other cases are extremely expensive and the quality of the products can be enough taking into account that the starting material is not GMP grade (fat tissue, corneas, bone, etc) and quality controls are performed at different stages of the manufacturing process as well as in the finished product. – Particularly in early stages it is difficult to have only one batch per incubator. It should be allowed to share the equipment. In order to minimize the cross-contamination risk, additional measures can be established, e.g. different coloured labels can be used to identify the different batches. – In early phases of clinical research (clinical trial phases I/II) when the manufacturing activity is very low, annual calibration, inspection or checking should only be asked for the facility, cabinets, incubators, air sampler and particle counters. The rest of equipment could be tested less frequently based in a risk-based analysis.
	Q3. How should the quality systems established in accordance with Directive 2004/23 be recognised in terms of GMP compliance for products that are ATMPs solely because the use of the relevant cells/tissues is for a different essential function in the recipient as in the donor (i.e. the manufacturing process does not involve any substantial manipulation)? What about the JACIE accreditation system?

	Answer: Yes, we consider that the quality systems and requirements (including air classification) for non-substantially manipulated ATMPs should be those established in Directives 2004/23/EC and 2006/86/EC. Consequently, we agree that JACIE standards and JACIE accreditation system should be recognised in terms of GMP compliance for non-substantially manipulated ATMPs. **Comment**: 1. Lines 79-80: The requirements for the processing of cell-based medicinal products considered medicinal products in virtue of its indication (according to criteria of same/different essential function) but which are not subject to substantial manipulation, should be those established in Directives 2004/23/EC and 2006/86/EC for the processing of cells and tissue for transplant in tissue establishments (JACIE standards). We believe that, from a risk/benefit analysis, it is disproportionate to ask for the same requirements and quality controls as in the case of substantially manipulated medicinal products. The products which best might illustrate this statement are the different fractions of bone marrow cells used for the treatment of those diseases different from the hemato-immunologic ones. The simple cell selection, either by physical methods (to obtain mononuclear cell fraction) or by inmunomagnetic methods (to obtain cell fractions such as CD133+ or CD34+ lymphocytes), is considered a non substantial manipulation by the advanced therapy's European Regulation itself. They are a group of cell products which have a double classification either as a transplant -when administered for the treatment of patients with hemato-immunologic diseases- or as a medicinal product -when administered for the treatment of diseases different from the formerly mentioned-. However, the product and its processing is the same in both cases. Therefore, if the accumulated experience throughout more than 50 years in the field of hematopoietic progenitor transplantation (HPT) has demonstrated the safety of the quality standards applied to the tissue establishments and the cell and tissue processing for transplant, it does not make sense to increase those manufacturing standards and demand greater quality controls for the same product just because the indication has changed. And specially, if we take into account that the HPT is generally allogeneic and it is performed in immunodepressed patients, whilst the cell therapy with the same product is normally autologous and used in immunocompetent patients.
SECTION 3. Personnel	Q4: Are the requirements laid down in Section 3 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?). Please provide comments on the text below as appropriate.
	Answer: Most requirements as laid down in section 3, Personnel, seem to be appropriate. The main areas where section 3 could be further developed are explained in the following comments. **Comments**: 1. Lines 133-134: There should be appropriate training in the requirements specific to the manufacturing and testing of the product as well as detailed hygiene programs. Proposed change: There should be appropriate training in the requirements

	specific to the **Advanced Therapy** manufacturing and testing of the product as well as detailed hygiene programs. 2. Lines 152-154: Because of their essential role in the quality system, the person responsible for production, the person responsible for quality control and the Qualified Person ("QP") should be appointed by senior management. Proposed change: Because of their essential role in the quality system, the person responsible for production, the person responsible for quality control and the Qualified Person ("QP") **if different should be duly appointed.** 3. Proposed addition: **The training and qualification required to be Qualified Person should be related to ATMPs.** Justification: Directive 2001/83/EC specifies the qualifications as well as the theoretical and practical study required to be a Qualified Person and the subjects required are not adapted to ATMPs. It would be useful to include this statement in the GMPs for ATMPs. **Notes:** 1.-**For non substantially manipulated ATMPs, JACIE standards should apply.** 2.-**For ATMPs at early clinical research (Phase I-II clinical trials):** Lines 129-130 & 155-156. In case of GMP facilities manufacturing only a very small number of batches per year for phase I/II clinical trials, for routine task that do not involve decision-making processes, under supervision and with appropriate training, it could be considered adequate to share personnel under the production and quality control areas.
SECTION 4. Premises	Q5: Are the requirements laid down in Section 4 sufficiently well-adapted to the specific characteristics of ATMPs? Please provide comments on the text below as appropriate.
	Answer: Most requirements as laid down in section 4, Premises, seem to be appropriate. The main areas where section 4 could be further developed are explained in the answers to questions 5 and 6. **Note: For non substantially manipulated ATMPs, JACIE standards should apply.**
	Q6: Do you consider that there are additional flexibilities that could be applied in connection with the requirements related to premises without compromising the quality of the ATMPs manufactured for commercial purposes?
	Answer: No, we agree with the proposal. We only have one comment. **Comment**: 1. Lines 179-181: The manufacture of technical poisons, such as pesticides and herbicides, or cytotoxic agents, should not be allowed in premises used for the manufacture of ATMPs. Nevertheless, some cytotoxic agents can be necessary to manufacture ATMPs, e.g. mitomycin, considered a cytotoxic agent, is necessary in the manufacturing process of some specific ATMPs. Proposed addition: The manufacture of technical poisons, such as pesticides and herbicides, or cytotoxic agents, should not be allowed in premises used for the manufacture of ATMPs. **Nevertheless the use of cytotoxic agents might be allowed for manufacturing ATMPs when necessary.**
	Q7: Do you consider that there are additional flexibilities that could be applied in connection with the requirements related to

	premises without compromising the quality of investigational ATMPs? If appropriate, please consider possible differences between first-in-man clinical trials and pivotal clinical trials.
	Answer: Yes, there might be additional flexibilities. Please see cooments. **Comments**: Besides the comment included in question 6, due to the size and location of most Academic GMPs in Europe, it would be useful to consider the following flexibilities: 1. Lines 176 to 178: Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as transit area by personnel who do not work in them. Proposed change: Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as transit area by personnel who do not work in them. **If such is unavoidable, appropriate control measures should be applied.** 2. Line 228 to 229: "…These pressure cascades should be- clearly defined and continuously monitored with appropriate methods alarm settings. Proposed change: "…These pressure cascades should be clearly defined and **monitored with appropriate methods.** 3. Lines 256 to 258: Where quarantine status is ensured by storage in separate areas, these areas must be marked and their access restricted to authorised personnel. Proposed change: Where quarantine status is ensured by storage in separate areas, these areas **should** be clearly marked ~~and their access restricted to authorised personnel~~.
	Q8: Should the use of a clean room with an A grade with a background of C or D grade be allowed for early phases of clinical trials (with the exception of gene therapy investigational medicinal products), provided that the specific risks are adequately controlled through the implementation of appropriate measures? Please substantiate your response. In particular, if you consider this option should be introduced, please address the benefits of introducing such flexibility and explain what measures could, in your view, be applied to avoid cross-contamination having regard to the potential risks (e.g. the level of cell manipulation, the use of processes that provide extraneous microbial contaminants the opportunity to grow, the ability of the product to withstand purification techniques designed to inactivate or remove adventitious viral contaminants, etc.)
	Answer: We consider that a background C or D could be allowed depending on the type of manipulation, the equipments for processing and the degree of development: 1. For non substantially manipulated ATMPs, irrespective of the degree of development (early phases, pivotal clinical trials or commercial production), the requirements established in Directive 2006/86/EC should apply, therefore background D should be allowed. The reasons have been explained in the answer to question 3. 2. For substantially manipulated ATMPs, we consider background B should be required. Nevertheless, in very specific circumstances, for early phase clinical development, it could be allowed a background C or D, provided the manipulation is not very extensive, an adequate risk evaluation has been performed and adequate quality controls have been set. This would

	facilitate translational research and first in human use of ATMPs, what could make the products more attractive for commercial partners to further develop them under more stringent requirements. 3. For ATMPs (substantially and non-substantially manipulated) processed in closed systems or isolators it should be allowed a background C or D, including gene therapy investigational medicinal products. **Comment**: Line 232-233: In general, an A grade with a background of B grade is required for pivotal clinical trials and commercial production. Proposed change: An A grade **can be followed for different backgrounds (B, C or D) depending on the type of manipulation, the equipments for processing and the degree of development**.
SECTION 5. Equipment	Q9: Are the requirements laid down in Section 5 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate
	Answer: We consider Section 5 is appropriate but allows different interpretations between National Competent Authorities. In principle the text makes the requirements apparently very flexible but discretional to the interpretation of National Competent Authorities. It could lead to the establishment of very restrictive requirements. **Comments**: 1. Lines 283-284: Primary containment should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment. More clarification would be appreciated. Does it refer to cabinets, isolators or other different equipments? 2. Lines 288-293: Automatic, mechanical or electronic equipment, including computers shall be routinely calibrated, inspected or checked to ensure proper performance. Written records of those checks shall be maintained. Proposed addition: **In early phases of clinical research (clinical trial phases I/II) when the manufacturing activity is very low, annual calibration, inspection or checking should only be asked for the facility, cabinets, incubators, air sampler and particle counters. The rest of equipment could be tested less frequently based in a risk-based analysis.**
SECTION 6. Documentation	Q10: Are the requirements laid down in Section 6 sufficiently well-adapted to the specific characteristics of ATMPs? Please provide comments on the text below as appropriate.
	Answer: Most requirements as laid down in section 6, Documentation, seem to be appropriate. The main areas where section 6 could be further developed are explained in the following comments. Additional flexibilities could also be introduced (please see answer to question 12). **Comments**: 1. Lines 332-333: it would be helpful to define what should be considered as substantial modifications in the manufacturing process of an investigational ATMP.

	2. Line 395: total quantity received. Proposed change: total quantity received**, only if relevant**. 3. Line 427: More clarification is required. It is not clear what batch documentation refers to. Apparently there is a contradiction between paragraphs 427-428 and 438-441. According to those paragraphs it is not clear for the batch documentation or data the period to be kept. Does batch documentation referred in the first paragraph mean SOPs? Does the data referred in the second paragraph mean master manufacturing record? **Note: For non substantially manipulated ATMPs, JACIE standards should apply.**
	Q11: Do you consider that there are additional flexibilities that could be applied –without compromising the robustness of the quality system- in connection with the documentation obligations for ATMPs manufactured for commercial purposes?
	Answer: Yes, there might be additional flexibilities. Please see comment 2 on Q10.
	Q12: Do you consider that there are additional flexibilities that could be applied –without compromising the robustness of the quality system- in connection with the documentation obligations for investigational ATMPs? If appropriate, please consider possible differences between first-in-man clinical trials and pivotal clinical trials.
	Answer: Yes, there might be additional flexibilities. The main areas where section 6 could include additional flexibilities are explained in the following comments. **Comments**: 1. Lines 337-339: In the case of investigational ATMPs, it should always be considered acceptable for the manufacturer to rely on the certificate of analysis of the supplier. The manufacturer should verify that the results recorded in the analysis certificate fit within the acceptance criteria. 2. Lines 341 and 351: At early stages of development (Phase I/II clinical trials) it might not be possible to define a maximum period of storage for some biological materials. Initial clinical trials will help to know it.
SECTION 7. Starting and raw material	Q13: Are the requirements laid down in Section 7 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate.
	Answer: We consider Section 7 is not sufficiently well-adapted to the specific characteristics of ATMPs, especially of autologous products and also at early stages of development. Additional flexibilities could be applied. Please see comments. **Comments**: 1. Lines 443-445: The quality of starting and raw materials is a key factor to consider in the production of ATMPs. Particular attention should be paid to avoid contamination and to minimise as much as possible the variability of the starting and raw materials. This paragraph is appropriate but allows different interpretations between National Competent Authorities. In principle the text makes the requirements apparently very flexible but discretional to the interpretation of National Competent Authorities. It could lead to the establishment of very restrictive requirements. Here there are some examples:

	– In first steps of the manufacturing processes of a single batch of ATMPs, small volume of culture media and supplements are needed. To optimize its use, aliquots should be allowed. Quality controls of these aliquots, if required, should be proportionate as the quality of the raw material is certified and quality controls are performed at different stages of the manufacturing process as well as in the finished product. – It is very difficult to minimize variability of human starting material when it is composed of tissues or cells. E.g.in the case of adipose tissue, availability of abdominal fat tissue is highly heterogeneous (patients with some diseases, such as ALS, have very small abdominal adipose tissue and surgeons must obtain it from different anatomic localizations to comply with specifications of weight). Composition of this fat tissue is also highly heterogeneous between patients, depending on age and nutrition. Sometimes, to minimize variability, authorities establish very narrow ranges (e.g. "weight ranges of starting material"). For clinical trials in early stages of development, wider ranges should be allowed, because they provide essential information of the limits of the manufacturing process that will help in its future development. – In the case of growth supplements, such as fetal bovine serum (FBS) or platelet lysate (hPL), it is almost impossible to acquire only one batch of these products to perform the manufacturing processes of all the batches necessary to complete the clinical trial along two or three years. For academic centres it is difficult to assess lot-to-lot variability of FBS or hPL and their impact on the finished products. – Quality requirements for non commercial platelet lysate from platelet units obtained in authorized blood banks, should follow transfusion standards. – It should be explicitly allowed the use of research-grade raw materials at early stages of development. Sometimes there are no GMP grade raw materials and in other cases are extremely expensive and the quality of the products can be enough taking into account that the starting material is not GMP grade (fat tissue, corneas, bone, etc) and quality controls are performed at different stages of the manufacturing process as well as in the finished product. 2. Lines 443–445: Prior to introduction in the manufacturing process, the conformity to the relevant requirements should be checked (identity, temperature control, etc). Proposed change: to eliminate this sentence because it is not clear what does check means. We consider it should be enough what we have proposed in section 6: The manufacturer should verify that the results recorded in the analysis certificate fit within the acceptance criteria. Additionally, lines 291-293 specify that equipments have to be checked. 3. Lines 491-492: it is important to ensure that antibiotics do not interfere with the sterility testing, and that they are not present in the finished product. Proposed change: it is important to ensure that antibiotics do not interfere with the sterility testing, and that they are not present in the finished product **unless it is necessary, provided they do not interfere with the sterility test**. **Note: For non substantially manipulated ATMPs, JACIE standards should apply.**

SECTION 8. Seed lot and cell bank system	Q14: Are the requirements laid down in Section 8 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trial)? Please provide comments on the text below as appropriate
	Answer: We consider Section 8 is not sufficiently well-adapted to the specific characteristics of ATMPs, especially at early stages of development. Additional flexibilities could be applied. Please see comments. **Comments**: 1. Lines 522-524: The number of generations (doublings, passages) between the seed lot or cell bank, the active biological substance and the finished product should be consistent with specifications in the marketing authorisation/clinical trial authorisation: – The subject-to-subject variability should be considered when establishing the number of generations. The necessity of process standardization to make the manufacturing process as reproducible as possible, usually leads to set as much detailed as possible specifications with narrow ranges for acceptance criteria. In early phases of clinical research (clinical trial phases I/II) it should be defined a maximum number of doubling or passages but not a fixed number or very wide range of generations. Initial clinical trials will help to better define the number of generations. 2. Lines 545 to 546. The storage temperature should be recorded continuously and, where used, the liquid nitrogen level monitored. Proposed change: The storage temperature should be **controlled and/or routinely checked**. 3. Lines 552 to 553. Once containers are removed from the seed lot/cell bank management system, the containers should not be returned to stock **if damaged or manipulated**. 4. Lines 554 to 555. In exceptional justified cases, it might be possible to accept the use of cell stocks/cell banks and viral seed stocks that were generated without full GMP compliance (e.g. xenogenic feeder layer generation). **Note: For non substantially manipulated ATMPs, JACIE standards should apply.**
SECTION 9. Production	Q15: Are the requirements laid down in Section 9 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate
	Answer: We consider Section 9 is not sufficiently well-adapted to the specific characteristics of ATMPs, especially at early stages of development. Additional flexibilities could be applied. Please see comments. **Comments**: 1. Lines 580 to 581**:** Any necessary in-process controls and environmental controls should be carried out and recorded. Proposed addition***:*** **In early clinical trials (phase I/II) non viable particles in Grade A should be continuously monitored in operation only when a critical process is being performed. Viable particles can be monitored at rest using air sampling.** 2. Lines 606 to 609. Proposed addition: **In early clinical trials (phase I/II), labelling could not be required provided that**

	materials, equipments and premises used for a batch were clearly recorded (for example in the batch record) to maintain traceability. 3. Line 628 to 629: The manufacture of the active substances and finished products should be separated from the manufacturing of other active substances/products, either in place or in time. Proposed change: **It is possible to manufacture different active substances/product in the same place or time without compromising product quality if correct measures are taken to avoid the risk of mistakes and cross-contamination (e.g. using campaigns).** A facility with premises well designed for multiproduct production, where the number of workers is appropriate, the personnel is well trained and fluxes are clearly defined is prepared to manufacture distinct products in the same place or time with minimal risk for product quality. On the other hand, the manufacture process of some ATMPs lasts for months. Dedicated facilities where no other product can be produced at the same time hamper the economical viability of the companies and non-profit organizations working on this kind of ATMPs. 4. Lines 648 to 649: For cell-based products, cleaning validation between the manufacturing of different batches should be performed. Proposed change: For early clinical trials it should be eliminated the validation: **In early clinical trials (phase I/II), cleaning between the manufacturing of different batches should be performed.** The cleaning validation performed before and during the manufacturing process validation should be considered sufficient. 5. Lines 687 to 689: Finished products should be held in quarantine until their final release under conditions established by the manufacturer in accordance with the terms of the marketing authorization or the clinical trial authorisation. Proposed change: Finished products should be held in quarantine until their final or **early** release under conditions established by the manufacturer in accordance with the terms of the marketing authorization or the clinical trial authorisation. Some ATMPs have to be released before obtaining the results of certain quality controls (typically sterility) because of the short lifespan of the product. 6. Lines 694 to 697. Rejected materials should be clearly marked as such and stored separately in restricted areas. Starting and raw materials should either be returned to the suppliers or, where appropriate, destroyed. Whatever action is taken, it should be approved and recorded by authorized personnel. Proposed change: **In early clinical trials (phase I/II),** rejected materials should be clearly marked and **storaged in specific areas**. Starting and raw materials should either be returned to the suppliers or, where appropriate, destroyed. **Note: For non substantially manipulated ATMPs, JACIE standards should apply.**
SECTION 10. Qualification and validation	Q16: Are the general principles laid down in Section 10 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate
	Answer: We consider Section 10 is not sufficiently well-adapted to the specific characteristics of ATMPs at early stages of

	development. Additional flexibilities could be applied. Please see comments. **Comments**: 1. Lines 711-713: The manufacturing process for investigational ATMPs is not expected to be validated to the extent necessary for commercial ATMPs but it is expected that premises and equipment are qualified (*i.e.* that it is verified that they comply with the specified requirements). Proposed change: The manufacturing process for investigational ATMPs is not expected to be validated to the extent necessary for commercial ATMPs **being acceptable in some cases a concurrent validation**. It is expected that premises and equipment are **calibrated, inspected or checked to ensure proper performance.** 2. Line 713: Proposed addition: **In early phases of clinical research (clinical trial phases I/II) when the manufacturing activity is very low, annual calibration, inspection or checking should only be asked for the facility, cabinets, incubators, air sample and particle counters. The rest of equipment could be tested less frequently based in a risk-based analysis.** 3. Line 715: Validation of aseptic processing should include a process simulation test using a culture medium (media fill test). Proposed addition: **In early clinical trials (phase I/II) it should be allowed to run this validation only when manufacturing process is defined and when significant manufacturing changes are introduced or new manufacturing personnel is incorporated.** **Note: For non substantially manipulated ATMPs, JACIE standards should apply.**
	Q17: Due to the biological variability inherent in ATMPs and limited batch sizes, process validation is particularly challenging for ATMPs. A pragmatic approach as to the specific requirements on validation should be developed. Please provide suggestions.
	Suggestion: – The necessity of process standardization to make the manufacturing process as reproducible as possible, usually leads to set as much detailed as possible specifications with narrow ranges for acceptance criteria. The specifications for finished products should be defined allowing a range according to the subject-to-subject variability. The validation protocols should accept, when necessary, broad ranges for starting materials and for finished products taking into account potential ethical issues (for example when patients have undergone surgery for procurement and have no other therapeutic options, as is the case of the procurement of fat tissue in patients with some diseases, such as ALS, who sometimes have very small abdominal adipose tissue and surgeons must obtain it from different anatomic localizations to comply with specifications).
SECTION 11. Qualified person and batch release	Q18: Are the requirements laid down in Section 11 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate

	Answer: Most requirements as laid down in section 11, Qualified person and batch release, seem to be appropriate. Additional flexibilities could also be introduced (please see comments). **Comments**: 1. Line 730: Each manufacturing site in the EEA must have at least one Qualified Person ("QP"). Proposed addition: **It could be acceptable to share the QP in more than 1 manufacturing site with a very low activity in manufacturing investigational ATMPs for early clinical trials (Phase I/II), provided the geographical proximity.** 2. Lines 768-769: QPs must have detailed knowledge of the product type and manufacturing steps for which they are taking responsibility. Proposed addition: **The training and qualification required to be Qualified Person should be related to ATMPs.** Justification: Directive 2001/83/EC specifies the qualifications as well as the theoretical and practical study required to be a Qualified Person and the subjects required are not adapted to ATMPs. It would be useful to include this statement in the GMPs for ATMPs. **Note: For non substantially manipulated ATMPs, JACIE standards should apply.**
SECTION 12. Quality Control	Q19: Are the requirements laid down in Section 12 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate
	Answer: We consider Section 12 is not sufficiently well-adapted to the specific characteristics of ATMPs, especially at early stages of development. Please see comments. **Comments**: 1. Lines 894-896: The manufacturer of an ATMP should have a person responsible for quality control that is independent from production. The independency of quality control from production is fundamental. Proposed addition: **In case of GMP facilities manufacturing only a very small number of batches per year for phase I/II clinical trials, it could be considered adequate to share personnel under the production and quality control areas for routine task that do not involve decision-making processes, under supervision and with appropriate training.** 2. Lines 924-925: Samples should be representative of the batch of materials or products from which they are taken. Proposed change: Samples should be representative of the batch of materials or products from which they are taken **if possible**. Related to retention samples, is not possible to retain a fully packaged unit from a batch, also in some cases, a representative sample is not possible. E.g. In some TEP is not possible to retain samples of finished products due to the instability of some components (matrix, scaffolds..). In this case it's only possible retaining samples of intermediate product (cell lines used for the manufacturing of the finished product) 3. Lines 928-929: Sampling of primary packaging and critical raw material should be kept. Proposed change: Sampling of primary packaging and critical raw material should be kept **whenever is possible**.

	4. Line 940: For investigational ATMPS, samples of starting materials should be kept for two years... Proposed change: For investigational ATMPS, samples of starting materials should be kept **if possible** for two years... 5. Lines 954-956: Identity testing of starting materials, release testing of the active substance/intermediates/finished products, and stability testing should be performed in accordance with the terms defined in the marketing authorisation/clinical trial authorisation. Proposed addition: **In the case of investigational ATMPs, it should always be considered acceptable for the manufacturer to rely on the certificate of analysis of the supplier. The manufacturer should verify that the results recorded in the analysis certificate fit within the acceptance criteria.** 6. Lines 1001-1002: After the marketing authorization is granted, the stability of the medicinal product should be monitored according to a pre-established program designed to detect any stability issue. Proposed addition: **However for investigational ATMPs or when shelf-life of the medicinal product is limited, stability analyses are not required**. 7. Additional comment: It should be specified that, **in early clinical trials (phase I/II), growth promotion tests should not be required in batches of settle plates and contact plates used to perform environmental monitoring**. The growth promotion test performed by the supplier should be sufficient. **Note: For non substantially manipulated ATMPs, JACIE standards should apply.**
SECTION 13. Outsourced activities	Q20: Are the requirements laid down in Section 13 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?). Please provide comments on the text below as appropriate.
	We have no comments about this question and the chapter 13. All the information is coherent and equivalent to the JACIE standards.
SECTION 14. Quality defects and products recalls	Q21: Are the requirements laid down in Section 14 sufficiently well-adapted to the specific characteristics of ATMPs (including regarding the early stages of development, i.e. first-in-man clinical trials?)? Please provide comments on the text below as appropriate.
	Answer: Yes, the requirements as laid down in section 14, Quality defects and products recalls, seem to be appropriate. We only have one comment. **Comment**: Lines 1054-1056: There should be established written procedures for recall of products, including how a recall should be initiated, who should be informed in the event of a recall (including relevant authorities), and how the recalled material should be treated. Proposed change: There should be established written procedures, **if it is possible**, for recall of products, including how a recall should be initiated, who should be informed in the event of a recall (including relevant authorities), and how the recalled material should be treated. Example: in the case of autologous cell therapy products, they are released once they comply with all the specifications but sterility. Results of sterility tests are obtained seven days after the product has been infused, so there is no

	possibility of recall). **Note: For non substantially manipulated ATMPs, JACIE standards should apply.**
SECTION 15 Environmental control measures for gene therapy products	**Comment**: It would be useful some guidance to be adapted for particular cases.
SECTION 16. Reconstitution of product after batch release	Q22: Do you agree with the principle that, where reconstitution of the finished ATMP is required, the manufacturer's responsibility is limited to the validation of the process of reconstitution and the transmission of detailed information about the process of reconstitution to the users?
	Answer: No, we do not agree. When a reconstitution of the finished ATMP is required, the manufacturer and/or sponsor must participate in training to the personnel involved to guarantee a correct administration of the ATMP. There should be a record of reconstitution operations, including the person who performs it and made critical operations.
	Q23: Do you agree with the principle that reconstitution is not manufacturing and therefore is outside GMP?
	Answer: Yes, we agree, these operations are not the responsibility of the manufacturer, however training, and custody of the records are his responsibility. This responsibility could be shared with the sponsor or with the holder of marketing authorisation.
	Q24: What activities should, in your view, be considered as reconstitution?
	Answer: We do not consider thawing as a reconstitution. However, we consider reconstitution dissolving or dispersing the ATMP, diluting or mixing the ATMP with the patient's own cells and/or other substances added for the purposes of administration (including matrixes).
SECTION 17. Automated production of ATMPs	Q25: How do you think that the GMP obligations should be adapted to the manufacture of ATMPs through the use of automated devices/systems? Who should be responsible for the quality thereof?
	Answer: It depends on the type of manipulation performed by the automated device/system. Whether the manipulation is not substantial, GMP obligations should not apply but should applied those established in Directives 2004/23/EC and 2006/86/EC. In case of substantial manipulation: – There should be somebody, quality control manager or qualified person, responsible of the quality of the batches produced through the automated device. – Relevant quality controls should be performed for the release of each batch. – A quality management system should be established with the aim of maintaining traceability and recording the activities performed for the batch.